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CHEMICAL ACHIEVEMENT, AND HOPE FOR THE FUTURE

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The hundred years of existence of the Sheffield Scientific School of Yale University have witnessed the transition of chemistry from an essentially empirical and descriptive science to a largely exact and theoretical one. One hundred years ago the properties of many chemical substances had been investigated, the difference between elements and compounds had been recognized, analytical chemistry had been developed to such an extent as to be a reliable tool, many methods of synthesis of inorganic and organic substances had been discovered, and the foundations had been laid for an extensive chemical industry.

However, at that time, in 1847, the correct atomic weights of the elements had not yet been generally accepted, so that the formula of water was still written as HO by many chemists. The idea of valence had not yet been formulated--it was not until five years later that

the statement was first made (by H. Frankland in England) that atoms have a definite combining power, which determines the formulas of compounds. The first structural formulas for molecules were not drawn until 1858, when Archibald S. Couper introduced the idea of the valence bond; in the same year August Kekulé, in Germany, showed that carbon is quadrivalent. During the next half century ^{chemistry} developed very rapidly, to become the great science--and powerful art--that it now is.

Here in New Haven, where Josiah Willard Gibbs was born, studied, worked, and died, I can ^{best} illustrate the progress of chemical science during the past 100 years ~~best~~ by discussing chemical thermodynamics, the field of science that, in the words of Wilhelm Ostwald, was founded by Gibbs. In 1847 J. Willard Gibbs was a boy eight years old. The first law of thermodynamics--the law of conservation of energy--had not yet been accepted by physicists, although Joule had recently made his determination of the mechanical equivalent of heat. It was not until a year later, in 1848, that Herman Helmholtz recognized the importance of Joule's work and followed its implications through various problems in chemistry, physics, and biology. The second law of thermodynamics had been formulated by S. Carnot, in 1824, but it was not until 1851 that Lord Kelvin and Clausius combined it with the first law to produce the present science of thermodynamics, in its application to physical phenomena. Then in the period between 1873 and 1878 Willard Gibbs published his great papers dealing with the application of thermodynamics to chemical phenomena. Gibbs' work put the science of

chemical thermodynamics in nearly its final form; only one more great discovery remained to be made--that of the third law of thermodynamics, by W. Nernst at the beginning of the twentieth century.

Let us contrast the knowledge about a chemical reaction available in 1847 with that in 1947. In 1847 a reaction involving the conversion of certain reactant substances into certain products, such as nitrogen and hydrogen into ammonia, could be discussed only to the extent that direct experimental information obtained by observing the reaction itself was at hand. Only if the reactants had actually been observed to combine to form the products could it be said to be a possible chemical reaction. The amount of heat evolved or absorbed during the reaction would have been known only if the reaction had actually taken place, and the heat evolution or absorption had been measured. The question of increasing the yield of the product could not have been discussed at all--there was no knowledge as to whether increasing the temperature, increasing the pressure, or making other changes in the system would increase or decrease the amount of product obtained. In 1947 it is possible, from knowledge of the thermodynamic properties of the reactant substances and the products, to predict, for a reaction that has never been observed to occur, most of its important characteristics--the amount of heat that would be evolved or absorbed when the reaction takes place, and the extent ^{to which} ~~that~~ it would take place, in its dependence on temperature, pressure, concentrations of the reactants, and other factors. There still remains, however, one most important question to which a definite answer cannot in general be given. This is the question as to the rate at which the reaction will take place under given circumstances. We are not yet able

to make predictions about this rate of reaction, except for certain simple systems. The field of chemical thermodynamics is in nearly its final state of development; the field of chemical kinetics is just beginning to be developed.

Chemical thermodynamics, like nearly every other field of chemistry, has been influenced by the great progress that has taken place in extending our knowledge of atomic and molecular structure during the past few decades. The electron itself was discovered in 1897, and the atomic nucleus in 1911; since then a penetrating and detailed understanding of the electronic and atomic structure of matter has been obtained, and chemists are now able to talk about the atomic and electronic architecture of molecules and crystals almost as confidently as architects can talk about the structural elements of skyscrapers and bridges. By the methods of spectroscopy, x-ray diffraction, and electron diffraction ^{accurate} ~~determined~~ interatomic distances have been determined for thousands of substances. The magnitudes of the forces operating between the atoms have also been determined experimentally for very many molecules and crystals. Further information about the nature of substances has been obtained by the application of many different techniques of modern physics--the study of the diamagnetic, paramagnetic, and ferromagnetic properties of the substances, their electrical properties, the spectroscopy not only of the visible, infrared, x-ray, and ultraviolet regions but even, in recent years, of the microwave and long wave radio regions of the spectrum. The structural knowledge obtained in this way about molecules permits the calculation of thermodynamic properties for many substances.

A significant start has already been made on the task of

formulating a complete system of chemical thermodynamics of pure substances. This task involves the determination for each substance at one temperature of ^{its} ~~the~~ enthalpy, relative to the elements that compose it. It is further necessary to determine the entropy of the substance at one temperature, which can be done by any one of three methods, the measurement of a chemical equilibrium involving the substance and ~~and~~ other substances of known thermodynamic properties, the measurement of the heat capacity down to very low temperatures and the application of the third law of thermodynamics, or the calculation of the entropy from structural data obtained by spectroscopic and diffraction methods. Knowledge of the heat capacity of the substance over a wide range of temperatures, obtained either by direct experiment or by calculation from known structural properties, then permits the extension of the tables of thermodynamic properties over this temperature range. We may well expect that at some time in the distant future there will be available extensive tables of the enthalpy, entropy, and free energy of thousands of substances over wide ranges of conditions. There would then still remain, however, the problem of the thermodynamic properties of solutions, for which no such simple and inclusive set of data could be formulated.

It is interesting to note that, in a practical sense, the third law of thermodynamics differs from the first and second laws, in that it cannot be applied completely independently of structural considerations. In general, thermodynamic deductions are expected to be independent of any structural considerations, and to be reliable, provided only that true thermodynamic equilibrium has been approximated or achieved in the

experiment. Investigations carried out during the past twenty-five years, especially by Professor William F. Giauque, have shown, however, that the applications of the third law of thermodynamics to the calculation of entropy values for crystalline substances by measurements of heat capacity made to low temperatures are often in practice not reliable, unless some structural information about the residual entropy in the crystals at the lowest temperatures at which measurements are made is available. Thus simple substances such as hydrogen, carbon monoxide, nitrous oxide, and nitrogen dioxide have residual entropies of significant amount, caused by such structural features as a randomness of orientation of molecules in the crystal lattices. It may be said, with justice, that the experiments have not yet been carried out to sufficiently low temperatures, ~~or that suf-~~
~~ficiently low temperatures,~~ or that sufficient time has not been allowed for the crystals to achieve a state of true thermodynamic equilibrium; nevertheless, the practical problem still exists--the reliable application of the third law of thermodynamics requires a penetrating understanding of the structure of the crystalline substance under investigation.

(1) The recent decades have seen an extraordinary development of the art of cryogenics, the production of low temperatures. The pioneer work of Dewar was extended by Kamerlingh Onnes, whose feat of reaching a temperature as low as 0.71° K. seemed for many years to be incapable of significant betterment. Then, in 192⁴, William F. Giauque [✓] suggested and ^{later} put into practice the astounding new method of cooling by demagnetization, with which he and other investigators have been able to reach temperatures as low as about 0.001° K.

Although the production of low temperatures might well be considered to be a part of the science of physics, the fact that this final great achievement of reaching the temperature of 0.001° K. was made by a professor of chemistry, using a method invented by himself, has led me to include mention of it in my talk this evening. The work done by Professor Olanque illustrates the fact that the borderline between chemistry and physics is a difficult one to define, as is also the borderline between chemistry and biology. The logarithmic dependence of certain thermodynamic quantities on temperature is, of course, responsible for the great difficulty found in decreasing the temperature by successive factors of ten, and leads to the theorem of the impossibility of reaching the absolute zero itself. It has recently been pointed out to me by Professor Frans Simon² at Oxford, however, that we should not feel that there is an interesting portion of nature to which access is denied to man, namely, the portion of nature that deals with the properties of matter at temperatures lower than those that can ever be achieved in the laboratory. Professor Simon pointed out that the only low temperature range that is inaccessible to man is that in which no interesting phenomena occur, because if any phenomena were to occur, they themselves could be used as the method of achieving the low temperature.

Let us now return to the basis of chemistry--the atoms of the chemical elements. The last hundred years have seen the systematization of the elements through the periodic system of Mendeleev, the assignment of precise atomic weights to most of the known elements, the discovery of the elements predicted by the unfilled sequences in Mendeleev's table, as well as the unanticipated series of noble gases, and finally, in recent

years, the development of modern alchemy, the conversion of one element into another, and the artificial production of new elements. I need do no more than to refer to Professor Lawrence's lecture this afternoon, in which he has described the development of this most exciting field of science. Now that four transuranium elements have been reported, neptunium, plutonium, americium, and curium, we may look forward with confidence to the announcement that still more new elements have been made, and that practical methods of manufacture in large quantities of the most rare of the lighter elements have also been developed. We may well expect that in the future world nuclear chemistry will be found of the greatest value in many ways, not only ⁱⁿ by the production of new elements and ⁱⁿ by the use of radioactive elements as tracers, but also ^{in causing} ~~by the production~~ of new chemical reactions through the use of bombardment with high energy particles.

Inorganic chemistry has been making steady progress. The inorganic chemist of today has a great advantage over his fellow of preceding generations, in that he has a thorough understanding of the molecular structure of most of the substances with which he is working, and of the relation between the physical and chemical properties of the substances and their structures. An illustration of the usefulness of structural knowledge ^{is} provided by the recent development of substances that are similar to organic compounds, but with silicon atoms, which form the same tetrahedral bonds as carbon, in place of some or all of the carbon atoms. The first substance of this nature was made half a century ago. It had not been found possible to make in large quantities the substance diamond

which is a very useful material because it is the hardest of all known substances. However, it was found possible to make a new substance, with the same tetrahedral structure as diamond, but with half of the carbon atoms replaced by silicon atoms--the substance carborundum, which has now for many years found extensive use as an abrasive. Then it was found that other compounds of silicon could be made, the silicones, which have, in place of long chains of carbon atoms, chains of silicon atoms (usually with oxygen atoms interspersed, in a sort of ether linkage), with methyl groups or other side chains attached.³ The silicones have many very useful properties. They can be used as insulating lacquers, permitting electrical motors to be built for operation at much higher temperatures than with organic insulators; silicone rubber can be made, especially for use at higher temperatures than ^{those} withstood by ordinary natural rubber or synthetic rubber; some of the silicone oils have a very valuable property, that of changing their viscosity only a small amount with change in temperature--a property that seems to be due to the tendency of the molecules to coil into a roughly spherical shape at low temperatures, and hence to roll over one another relatively easily, whereas at higher temperatures, at which the molecules uncoil, they become entangled with one another, and thus overcome in large part the normal tendency of a liquid to show a pronounced decrease in viscosity with increase in temperature.

The chemistry of fluorine has made great progress in recent years. The valuable properties of new compounds of fluorine depend on the volatility of fluorine compounds and the low chemical reactivity of the carbon-fluorine bond. Useful fluorine compounds include the freons, such

as CF_3Cl_2 , which are used as the fluid in refrigerating machines and as non-toxic solvents for insecticides and other solutes, and the fluorine-carbon high polymers, such as the extremely unreactive phenolic that is formed by the polymerization of tetrafluoroethylene.

✓ An interesting recent development in inorganic chemistry is that of new techniques for growing large crystals for special purposes. During the war it was found possible to grow large crystals, weighing many pounds, of such substances as ethylenediammonium tartrate, valuable because of their piezoelectric properties, which find use in radar and other fields of modern physics. In Germany an interesting technique of growing large crystals of synthetic mica was developed, which depends for its success on the orientation of the growing crystal in a strong magnetic field.

The art of organic chemistry and the science of organic chemistry have moved along steadily hand in hand. Organic chemists develop a feeling for the chemical properties of the many substances with which they work which goes far beyond the systematized theoretical knowledge that they can express; but the theory of organic chemistry has nevertheless now developed to such a state that the science is no longer a mysterious one, purely an art whose practice depends on the application of empirical rules. It is now possible for the organic chemist to use his knowledge of molecular structure to predict, with some confidence, that certain reactions could be carried out to produce products with certain desired properties. One most interesting application of this new method in organic chemistry has been to the manufacture of high polymers, such as the new fibrous and plastic substances, which were synthesized in consequence

of predictions of their properties made upon the basis of considerations of molecular structure.

The methods used by the organic chemists became more powerful from decade to decade. He now has at hand techniques of very high pressure hydrogenation, the use of catalysts specific to certain reactions, powerful techniques of separation such as chromatographic analysis and molecular distillation, and new physical methods for structural studies such as x-ray diffraction and spectroscopy. A very interesting example of the interrelation between organic chemistry and other fields was provided during the war by the concerted attack on the problem of the structure of penicillin.⁴ The organic chemists who were working on the problem found it impossible to determine the correct structure by the conventional methods, because the molecule has some structural characteristics that have not appeared before in any known substances, and it remained for physical chemists and physicists, using the techniques of x-ray diffraction and infrared spectroscopy, to determine the structure for them.

It is the field of chemistry in relation to biology and medicine in which most striking progress has been made in recent decades, and which offers the most promise for the future. Biologists now are becoming chemists - they isolate vitamins, hormones, enzymes, acetylcholine in nervous processes, histamine in anaphylaxis and allergic responses, plant growth factors, wound healing substances, flowering substances, substances to hold the fruit on the trees and to ripen the fruit after it has left the trees. No longer is it possible for a chemist to achieve a feeling of superiority to the biologist simply by quoting ^{some} ~~from~~ complex chemical formulas - nor, indeed, for the physicist to overcome the chemist by quoting some complex mathematics.

And in medicine, as in biology, a new future is drawing near - a future of great progress through ever closer cooperation with the basic sciences. There has indeed been great progress in medicine during the past century. In forty years the mean expectancy of life has increased from 49 to 65 years. The childhood diseases - diphtheria, scarlet fever, whooping cough - have decreased to 10 percent of their mortality in a quarter of a century. Other infectious diseases are in the main well under control, by vaccines, serums, the sulfa drugs, and now penicillin. Shakespeare mentioned

"the rotten diseases of the south, the guts-griping, ruptures, catarrhs, loads o'gravel i' the back, lethargies, cold palsies, raw eyes, dirt-rotten livers, wheezing lungs, bladders full of imposthume, sciaticas, lime-kilns i' the palm, incurable bone-ache, and the rivelled fee-simple of the tetter."

Most of these diseases are no longer important - there are now no serious cases, so far as I know, of rivelled fee-simple of the tetter, but "incurable bone-ache," under which we might include arthritis, is a very serious disease, of which little control has been obtained. There are still virus diseases that are very troublesome - poliomyelitis, influenza, the common cold. Then there remains the problem of the degenerative diseases - cancer, heart disease, cerebral disease, nephritis - which, as control of other diseases is obtained, are becoming increasingly important. To attack these great medical problems new basic knowledge is needed, about the nature of cells and of physiological processes, and about the chemotherapeutic action, as well as the normal physiological action, of chemical substances.

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The greatest problem that remains to be solved is that of the structural basis of the physiological activity of chemical substances. When once this problem has been solved, and when it has become possible to determine in detail the molecular structure of the vectors of disease and of the constituents of the cells of the human body, we shall be able to draw up the specifications of the specific therapeutic agent to protect the body against a specific danger, and then to proceed to synthesize the agent according to the specifications. So far we have only the hint that chemotherapeutic agents may act through competition with essential metabolites, as in the competition, pointed out by Woods and Fildes,^g of the sulfa drugs with ^P_A aminobenzoic acid.

(5) I believe that this problem, that of the nature of the competition of two substances presumably for specific combination with some part of a living cell, is very closely related to the general problem of the nature of the forces that leads to the striking specificity of properties shown by many biological substances, especially the native proteins and polysaccharides. I believe that these forces are also operative in the phenomenon of self-duplication shown by viruses, genes, and other biological entities, and which will be discussed by Dr. Stanley and Professor Beadle in their lectures tomorrow. I myself have been especially interested in the specific forces operating between an antibody molecule and the molecules of antigens or haptens with which it has the power of specific combination. My interest in this problem was developed over ten years ago in conversations with Dr. Karl Landsteiner and the work that my collaborators and I have done has consisted largely in the extension and refinement of investigations initiated by Dr. Landsteiner. ~~He~~

Permit me to review briefly the basic phenomena of immunochemistry. When a foreign material of large molecular weight - a protein or polysaccharide, either pure or part of the structure of an animal or plant cell - is injected into an animal, such as a rabbit, the animal in the course of a few days may develop in its blood and within its cells/ substances, called antibodies, that have the power of specific combination with the injected material, the antigen. Thus when a particular animal or plant protein is injected into a rabbit, the rabbit develops in its blood antibodies that are capable of combining with that protein, but not, or at any rate only very exceptionally, capable of combining with any of the tens of thousands of other proteins that exist in nature. For example, an antiserum made by injecting hemoglobin obtained from one animal into a rabbit is able to combine with that form of hemoglobin, but not with hemoglobin obtained from the red cells of other animals, except those of very closely related species. The act of combination of antibody and its homologous antigen may be shown by several different phenomena, such as the agglutination of cells, in the case of a cellular antigen, the formation of a precipitate on mixing a solution of antigen and its homologous antibody, the allergic response of a sensitized animal on receiving a subsequent injection of the antigen, and the lysis or other changed behavior of cells to which antibody has attached itself.

The phenomena of immunochemistry raise two great questions. The first is that as to the nature of the forces between antibody and antigen, which leads to the power of selective combination of antibody and the homologous antigen and the rejection of other molecules, except those

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very closely related to the homologous antigens. The second problem is that of the mechanism of the manufacture of the antibody, and of its endowment with this power of specific combination. The great versatility of the living organisms in their production of specific antibodies was shown by the early work of Landsteiner with artificial conjugated proteins as antigens.⁷ Landsteiner found that it was possible to cause an animal to make antibodies with the power of specific combination with various chemical substances of known structure. He achieved this by attaching these chemical substances to a protein molecule, which was then injected ^{to} a rabbit. The rabbit, under the influence of the injected protein, produced an antiserum containing antibodies capable in general of combining with the particular protein that was used in making the artificial conjugated protein, and also capable of combining with the attached chemical substances. For example, an antiserum prepared by coupling diazotized p-aminobenzenearsonic acid with ovalbumin was found to form a precipitate strongly with this particular azoprotein, and also to precipitate, in smaller amounts, ovalbumin itself and also any azoprotein made by coupling diazotized p-aminobenzenearsonic acid with another protein, such as sheep serum albumin. The precipitation by the antiserum of such an azoprotein, in which the protein part is completely different from that of the immunizing azoprotein, is evidence that some of the antibodies in the antiserum have a specific combining power with the benzenearsonic acid group. Landsteiner and his collaborators were able in this way to prepare antisera containing antibodies with the power of specific combination with scores of different chemical substances, many of which could hardly be considered to have any

natural relation to the injected animal. These results showed that the versatility of the living organism in antibody production is very great, and made it probable that the antibody precursor was to be considered as a plastic material, able to be influenced by the injected antigen in such a way as to obtain directly from the antigen itself the property that leads to the power of specific combination with it.

Landsteiner and his collaborators also discovered and utilized an important phenomenon, that of hapten inhibition. ^B They found that, for example, when benzenearsonic acid itself is added to an antiserum made by injecting an azoprotein containing the p-azobenzenearsonic acid group no precipitate occurs, although a precipitate would be formed in the absence of the benzenearsonic acid. The benzenearsonic acid is thus shown to have the power of combining with antibody homologous to this haptenic grouping, to form a soluble complex. Information about the strength of the combination of the hapten and of the antibody can be obtained by seeing what concentration of hapten is necessary to prevent the precipitation of the antiserum with a hapten-homologous azoprotein. Landsteiner and his collaborators in this way obtained a great amount of qualitative information about the combining powers of various chemical substances with antibodies homologous to haptenic groups of known structure. They found, for example, that not only benzenearsonic acid but also various substituted benzenearsonic acids have the power of combining with anti-p-azobenzenearsonic acid serum and that the strength of the combination depends upon the nature of the group substituted in the benzene ring and on the position in which it is substituted. Thus in general a group substituted in the para position

is formed. Nevertheless, it can be deduced that combination has occurred between the benzenearsonic acid and the antibody, because on addition of an azoprotein containing the p-azobenzenearsonic acid group no precipitate

in benzenearsonic acid increases the combining power with anti-p-azobenzenearsonic acid serum, whereas the substitution of a group in the ortho or meta position decreases the combining power with these antibodies.

My collaborators (Professor Dan H. Campbell, David Pressman, Carol Ikeda, ^{Miyoshi} ~~Miyoshi~~ Ikawa, David H. Brown, John T. Maynard, Allan L. Grossberg, Stanley M. Swingle, John H. Bryden, Leland H. Pence, and Frank Lanni) and I have continued and extended this work, primarily by developing and using quantitative methods, permitting the determination of approximate values for the equilibrium constant of the reaction of combination of hapten and antibody. ⁹ We have also made use of a simplification in the experiments, involving the elimination of one protein from the precipitation test. Inasmuch as the structure of no protein is as yet ~~known~~ known, a precipitation reaction involving two proteins, the antibody and the asoprotein, is an especially complicated reaction to study, and the possibility of obtaining information about the antibody might well become greater if the other protein could be eliminated. Landsteiner and van der Schoer ⁸ observed that certain simple substances that they had prepared for use as hapten inhibitors themselves gave a precipitate with the hapten-homologous antisera. These substances were dyes obtained by coupling two or more haptenic groups together - an example would be resorcinol with two or three azobenzenearsonic acid groups attached to it. Many of our hapten-inhibition experiments have been carried out with use of precipitating polyhaptenic antigens of this type, the system under study then containing only one substance of unknown structure, the antibody itself.

Landsteiner's results could be interpreted in terms of our modern knowledge of atomic and molecular structure to permit a definite conclusion to be reached regarding the nature of the specific forces between antibody and antigen, and the structure of antibody molecule, and this conclusion has been strengthened by the additional information given by the experiments that my collaborators and I have carried out in Pasadena. ^{31D} The conclusion is that the specificity of ^{int} ~~interaction~~ of antibody and homologous antigen results from a detailed complementarity in structure, as was first suggested by Haurowitz and Breini ^H and by Jerome Alexander, ¹² and later emphasized by Stuart Hudd. ¹³ The complementarity in structure must be such as to permit a large portion of the surface of the antigen to be brought into juxtaposition with a corresponding portion of the surface of the antibody molecule. The weak forces that operate between any atom or small atomic group and adjacent atoms would then come into play between each surface atom of the antigen and the immediately adjacent atoms of the antibody; these weak forces, integrated over the juxtaposed surfaces, would produce a resultant force strong enough to lead to the formation of an effective bond. Inasmuch as most of the weak forces operating between atoms and small molecules fall off very sharply with increasing distance, an effective bond would be formed only if the two molecules were in contact with one another, that is, if the surfaces of the atoms of antigen and antibody were to be no more than a very few Angstroms apart. The specificity of the bond formed in this way would result from the detailed complementarity not only in general surface configuration but also in the positions of the groups capable of forming hydrogen bonds and in the positions of the positive

and negative electrical charges. It can readily be seen that this mechanism does provide the possibility of very great specificity. Thus a combining region with area of perhaps 200 square Angstroms, representing a surface of about fifty atoms, could be prevented from approaching to contact with the complementary region on the antibody simply by replacing a methyl group, say, on the antigen surface, by a phenyl group, which would extend about 3 Å above the former surface, and would hence hold the antibody 3 Å farther away from the antigen, thus reducing the forces of attraction to such an extent as no longer to permit them to result in a significant bond.

The approximation of the antibody to the haptenic group of the immunizing antigen must be very close. A striking bit of evidence, from among the great amount that exists, is that of the cross reactivity of two closely related haptenic groups, the m-aminobenzoic acid group and the 4-chloro-3-aminobenzoic acid serum precipitates readily both with the hapten-homologous azoprotein and with an azoprotein containing the ^m-azobenzoic acid group. On the other hand, the anti-m-azobenzoic acid serum precipitates readily an azoprotein containing the m-azobenzoic acid group, but does not form a precipitate with an azoprotein containing the 4-chloro-3-azobenzoic acid group. The explanation that we propose of this cross reactivity between one antiserum and the substituted azoprotein but not between the other antiserum and the different azoprotein is that the phenomenon depends upon the fact that the chlorine atom is much larger than the hydrogen atom that it replaces, the van der Waals radius of chlorine being about 1.8 Å, and that of hydrogen only about 1.2 Å. If it

group, which differs from the first only in having a chlorine atom in place of the hydrogen atom. Landsteiner and his collaborators found that anti-4-chloro-3-aminobenzoic acid

is assumed that the combining region of an antibody fits tightly about the haptenic group of the immunizing antigen, the anti-4-chloro-3-azobenzoic acid antibodies would contain in the appropriate place a cavity into which a chlorine atom could fit, along with the rest of the haptenic group. This cavity, with radius 1.8 \AA , would be large enough to accept easily a hydrogen atom in the unsubstituted azoprotein, and the replacement of chlorine by hydrogen would have no effect other than to decrease slightly the force of attraction between the haptenic group and the antibody, as a result of the smaller van der Waals attraction of a hydrogen atom and of a chlorine atom for surrounding atoms. On the other hand, the cavity in the anti-m-azobenzoic acid antibody is required only to be large enough to receive a hydrogen atom with van der Waals radius 1.2 \AA . There might well then be a considerable amount of a steric strain if the 4-chloro-3-azobenzoic acid haptenic group were to be forced into this cavity in the antibody, and the steric strain might be great enough to decrease the combining power to such an extent that no precipitate would be observed by the investigators.

This experimental result indicates that the fit of antibody to antigen is, in some cases at least, a very close one, so that a difference in atomic radius of 0.6 \AA is significant. Our quantitative investigations in Pasadena provided a large amount of evidence substantiating this conclusion. ^{NY} One extensive series of investigations was made of the combination of antigens homologous to the o-benzenearsonic acid haptenic group, the m-azobenzenearsonic acid group, and the p-azobenzenearsonic acid group. It was found that in each case the substituted benzenearsonic acids with the

substituent in the same position as the azo group of the immunizing azo-protein combine more strongly with the antibody than those with the substituent group in a different position, and the conclusion was reached from the values of the hapten inhibition constant that the surface configuration of the combining regions of the antibody molecules approximates that of the haptenic group to within closer than 1 Å. A similar conclusion has also been reached by a study of the effect of electrical charge. The ratio of inhibiting powers of two similar haptens, one containing a positively charged group, the trimethylammonium ion group, and the other the uncharged group with the same size and shape, the tertiary butyl group, with anti-serum made by injecting rabbits with sheep serum with attached p-azobenzene-trimethylammonium ion groups, could be interpreted to show that the positive charge of the charged haptenic group interacts with a negative charge in the antibody 7 Å away. Inasmuch as the positive charge in the phenyltrimethylammonium ion may be considered to be at the center of the nitrogen atom, and the radius of this ion (the distance from the center of the nitrogen atom to the surface of the methyl groups) is 3.5 Å, and that also the minimum distance of approach of a negative charge to the surface of the antibody may be taken as the radius of an oxygen atom, 1.4 Å, the minimum distance of approach of a positive charge in the hapten and a negative charge in the antibody is calculated to be 4.9 Å. The fact that the value calculated from the hapten-inhibition data is only 2.1 Å greater than this again indicates that in general there is a very great complementariness in structure and closeness of fit of antibody and antigen.

It is my opinion that the general problem of the nature of specific biological forces has thus been solved, and that with the extension of our knowledge of detailed atomic structure of proteins and other biological

substances we may hope that this understanding, ~~of the nature of specific biological forces~~ will permit a more effective attack on many of the problems of biology and medicine.

I should like now to discuss a closely related question - that of the nature of enzymes and of catalysts in general. In order to function, the living cell carries out many specific chemical reactions that do not take place when the reactants are simply mixed with one another. These reactions occur in nature because there are present molecules of a specific catalyst, the enzyme appropriate to the reaction. I believe that an enzyme has a structure closely similar to that found for antibodies, but with one important difference, namely, that the surface configuration of the enzyme is not so closely complementary to its specific substrate as is that of an antibody to its homologous antigen, but is instead complementary to an unstable molecule with only transient existence - namely, the "activated complex" for the reaction that is catalysed by the enzyme. The mode of action of an enzyme would then be the following: the enzyme would show ~~possibly~~ a small power of attraction for the substrate molecule or molecules, which would become attached to it in its active surface region. This substrate molecule, or these molecules, would then be strained by the forces of attraction for the enzyme, which would tend to deform it into the configuration of the activated complex, for which the power of attraction by the enzyme is the greatest. The activated complex would then, under the influence of ordinary thermal agitation, either reassume the configuration corresponding to the reactants, or assume the configuration corresponding to the products. The assumption made above that the enzyme has a

configuration complementary to the activated complex, and accordingly has the strongest power of attraction for the activated complex, means that the activation energy for the reaction is less in the presence of the enzyme than in its absence, and accordingly that the reaction would be speeded up by the enzyme. My colleague Professor Carl Niemann and I are carrying out experiments on inhibition of enzyme activity designed to test this postulate, by the search for inhibitors that have a greater power of combination with the enzyme than have the substrate molecules themselves. This method of attack should, indeed, provide us with information about the nature of the active region of the enzyme, namely, that it is complementary to the configuration of the strong inhibitors.

This picture of the nature of enzymes may well make us optimistic about the future of chemotherapeutics, for it predicts that for every enzyme, and in particular for the enzymes that are essential for bacterial growth, it would be possible to find an inhibiting molecule which is more closely complementary in structure to the enzyme than is the substrate itself, and which would accordingly be an effective inhibitor. The picture even presents us with ideas as to the nature of substances which would be effective inhibitors - namely, that they should closely resemble the activated complex, intermediate in configuration between the reactants and the products of the catalyzed reaction. A possible practical application of this concept is that to penicillin and its destruction by the enzyme penicillinase. Some of the organisms that resist the bacteriostatic action of penicillin may achieve their resistance through the manufacture of penicillinase, which destroys the penicillin as it approaches the organism. If it were possible

to synthesize or to obtain by the degradation of penicillin itself a substance with molecular configuration such that it would combine with penicillinase more strongly than does penicillin, and thus would inhibit the action of the penicillinase, this specific inhibitor might be injected (or even taken by mouth) along with the penicillin, which might thus in this way increase its bacteriostatic action.

We have far less evidence bearing in a detailed way on the problem of the process of formation of complex biological molecules than on the problem of the nature of specific biological forces. Nevertheless, a reasonable proposal can be made as to the process of formation of these molecules, on the basis of the information available on the nature of the forces themselves, and the assumption that the known laws of molecular physics are applicable to biological systems. I shall illustrate this proposal by discussing a possible mechanism of formation of specific antibodies. * 10

* L. Pauling, J. Amer. Chem. Soc., 62, 2643 (1940).

The problem that we pose is the following: how is it possible for a cell to manufacture an antibody molecule with the power of specific combination with an arbitrarily chosen antigen? It might be that the difference in structure of the antibody molecule and a normal molecule of γ -globulin or an antibody molecule homologous to another antigen would result from a difference in the ordering of the amino-acid residues in the polypeptide chains, as was suggested by Breinl and Haurowitz and by Mudd. ** 14 16

** F. Breinl and F. Haurowitz, Z. physiol. Chem., 192, 45 (1930); S. Mudd, J. Immunol., 23, 423 (1932).

However, a simpler assumption is that all antibody molecules produced by the same protective mechanism in the cell contain the same polypeptide chains as the normal globulin and differ from normal globulin and each other only in the configuration of the chain, that is, in the way the chain is coiled in the molecule. It is much easier to devise a mechanism for causing the polypeptide chain to assume the desired one of the alternative configurations than to devise a mechanism for producing great variations in the ordering of the amino-acid residues. Moreover, the number of configurations accessible to a polypeptide chain containing a thousand or more amino-acid residues is so great as to provide an explanation of the ability of the animal to form antibodies capable of specific combination with a very great number of different antigens. Let us assume that a portion of a polypeptide chain, one end, say, which would be involved in the formation of a combining region of the antibody, is of such a nature that it is able to coil into any one of a large number of alternative configurations, all of which have very nearly the same energetic stability, so that the choice among them may be determined by relatively small changes in the environment, tending to stabilize one or another of the configurations. In the absence of an antigen the polypeptide chain would fold into the configuration that happens to be the most stable in the environment in the cell, and would produce a molecule of normal γ -globulin. In the presence of the antigen, however, the folding of the polypeptide chain would take place in a way determined to some extent by the interaction of the chain with the atoms in the surface of the antigen molecule. This interaction would find expression in the formation of that configuration

or those configurations of the polypeptide chain that permit the system as a whole to have the greatest stability. The greatest stability results, of course, from the formation of the strongest bond between the folded polypeptide chain and the antigen molecule. Accordingly, we have in this simple mechanism, involving the folding of a polypeptide chain into a structure whose nature is determined in considerable part by the presence of an antigen in the immediate neighborhood, a straightforward way of producing an antibody molecule with the power of specific combination with the particular antigen present, resulting from a complementariness in structure that is automatically assumed by the polypeptide chain that constitutes the combining region of the antibody molecule.

It is clear that the same mechanism, whereby one molecule present in the cell may influence the structure of another molecule that is being formed, may be invoked as an explanation of both hetero-catalytic and auto-catalytic activities of biological molecules in general. A gene may have the power of causing the synthesis of a certain protein molecule capable of acting as an enzyme catalysing a particular chemical reaction through its possession of a structure essentially complementary to that of the active region of the enzyme molecule, and which can act as a template in the production of that enzyme molecule. The power of self-duplication of the gene might well have a similar explanation - in case that the gene happens to be complementary to itself, then it could serve directly as the pattern for itself; or it might produce the same result, the manufacture of replicas of itself, by working through an intermediate complementary to itself, which then serves as the pattern for the new gene.

complementary to the intermediate and identical with the original gene. However, reliable information about the detailed nature of these fundamental molecular processes in biological systems must await further experimental study.

So far I have been discussing the least interesting aspects of the developments of chemistry in the future. These least interesting aspects are those that can be predicted, that can be foreseen on the basis of our present knowledge. They consist primarily of the results of application and development of the discoveries that have already been made. The great no one has yet thought about, the discoveries that discoveries of the future - those that will make the world different from the present world - are the discoveries that will in fact be made as soon as the idea underlying them take shape in the mind of some imaginative scientist. Who is there among us who ten years ago would have predicted that the field of nuclear structure and atomic energy would develop in the way that it has? Who can ^{now} say what the great discoveries of the next ten years will be?

I have talked about hope for the future - but the discoveries that we can ^{not} foresee may not all be obviously beneficial. Let me say, with Walt Whitman,

"I know I am restless and make others so,
I know that my works are full of danger, full of death,
For I confront peace, security, and all the settled laws,
to unsettle them....

the threat of what is call'd hell is little or
nothing to me,
And the lure of what is call'd heaven is little or nothing
to me;

Dear comrades! I confess I have urged you onward with me,
and still urge you, without the least idea what is
our destination,

Or whether we shall be victorious, or utterly quell'd and

defeated."

Science cannot be stopped. Man will gather knowledge no matter what the consequences - and we cannot predict what they will be. Science will go on - whether we are pessimistic or ^{are} optimistic, as I am: I know that great, interesting, and valuable discoveries can be and will be made, of the sort that I have just described - but I also know that still more interesting discoveries will be made that I have not the imagination to describe - and I am awaiting them, full of curiosity and enthusiasm.

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